

This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 License ([www.karger.com/OA-license](http://www.karger.com/OA-license)), applicable to the online version of the article only. Distribution for non-commercial purposes only.

# Hepatic Artery Chemoembolization for Hepatocellular Carcinoma Recurrence Confined to the Transplanted Liver

Brian I. Carr

Department of Nutrition and Experimental Biology, IRCCS Saverio de Bellis  
Medical Research Institute, Castellana Grotte, Italy

## Key Words

Hepatocellular carcinoma · Chemoembolization · Liver transplant · Tumor responses

## Abstract

**Background:** Careful hepatocellular carcinoma (HCC) case selection permits orthotopic liver transplantation with the expectation of around 70% plus 5-year survival. However, many patients have tumor recurrences and there is little literature guidance in the management of these patients.

**Aims:** A retrospective examination of patients transplanted with HCC who subsequently developed liver recurrence.

**Methods:** A case cohort series of patients was prospectively followed who had liver-only multifocal tumor recurrence of HCC after liver transplant and were then treated with chemoembolization.

**Results:** All 6 patients had recurrent HCC. 2 had no response, 1 had stable disease, 2 had partial response (PR) and 1 had complete disappearance (CR) of disease. Their survival (in months) was: 13 (no response), 18 (no response), 12 (stable disease), 19 (PR), 30 (PR) and 50 (CR). There were no liver toxicities.

**Conclusions:** Chemoembolization for tumor recurrence in the transplanted liver is as safe as or safer than in the pre-transplant liver, due to the absence of cirrhosis. In this series, there were 3 of 6 responses with some long survivors.

## Introduction

The Milan criteria established the long-term survival of patients with small hepatocellular carcinomas (HCC) after orthotopic liver transplantation (OLT) and have been a standard since publication [1], in contrast to the variable results for tumors larger than these criteria [2–4]. Despite the evident success of these criteria of one lesion <5 cm in diameter or 3 lesions, all <3 cm in diameter, some patients still have tumor recurrence. There has been no established treatment protocol for these patients. The benefits of chemoembolization include the treatment of a tumor in a non-cirrhotic liver. But the concerns include the possibility of damage to the hepatic artery with risk of damage or loss of the transplanted liver. The current case series describes the use of full-dose chemoembolization in 6 patients with HCC tumor recurrence confined to the liver after OLT and the long-term results.

## Methods

Six patients who had pathologically proven HCC and one patient with pathologically proven neuroendocrine liver tumors (without known primary) had uneventful OLT, followed by liver-only tumor recurrences, all within 24 months of OLT. All patients had normal serum bilirubin at the time of recurrence and CT scans of the chest, abdomen and pelvis showed tumor only in the liver. All had percutaneous biopsy proof of tumor recurrence. Each patient was treated with chemoembolization as previously described [5, 6] using cisplatin 125 mg/m<sup>2</sup>. All chemotherapy was administered together with Biospheres (Embospheres 100–300 μm) embolization particles. Treatments were repeated every 3–4 months until tumor stabilization or response, and thereafter only with evidence of tumor growth without metastases. Triphasic helical CAT scans (CT scans) were performed before every clinic visit, which was typically every 2–3 months. Tumor size responses were measured after CT scans and recorded according to RECIST criteria. Toxicities were evaluated using the NCI Common Toxicity Criteria v3. Patients were followed till death except one, who is alive at the time of writing.

## Results

### *Treatments and Responses to Chemoembolization*

All 6 HCC patients received single-agent cisplatin. The number of treatment cycles is shown in [table 1](#). The patient in whom there was complete tumor response (CR) received an additional 2 cycles of treatment after CR and then treatment was stopped and the patient was followed up at the clinic with CT scans. The other patients were treated till evidence of tumor progression or metastasis. All 6 patients were evaluable for tumor responses by CT scan. Table 1 shows that there was 1 complete response (CR), 2 partial responses, 1 patient with stable tumor and 2 without response whose tumors progressed on chemoembolization. Thus, 3/6 (50% of patients) had responses and 4/6 (66.6%) had disease control. This was similar to the response rates we have previously reported in the non-transplant setting [5, 6]. During the same time period, an additional 13 patients with HCC also recurred, but with metastases that were not limited to the liver and were not treated with chemoembolization.

### *Treatment Toxicities*

A single patient had a greater than grade 2 bilirubin toxicity, which was transient, returning to normal within 14 days of the peak. The subsequent chemoembolization cycle was administered at 50% dose reduction, without any toxicity. An additional 3

patients had grade 3 granulocyte toxicity, which normalized within 4 weeks and required no dose reduction. No adjustments to immunosuppression schedule or dosing appeared to be required as a result of the chemotherapy.

#### *Survival and Death*

All 6 patients eventually died from their tumors; 5 of them from new metastases while on therapy and 1 from progressive liver involvement by tumor. The one patient who had a CR subsequently developed lung metastases.

#### **Discussion**

The number of patients with HCC who are treated with liver transplantation is rising, especially given the long-term survival for patients with small tumors without metastases [1] and the increased priority given to these patients on the waiting lists for cadaveric organs, especially since the general use of the model for end-stage liver disease (MELD) in organ allocation. Several factors have been shown to be associated with an increased risk of tumor recurrence, including lymph node and vascular invasion [2], as well as tumor size, number and grade. The incidence of tumor recurrence seems to be around 20% [7–10], with significantly lower survival in patients with recurrence than in those without. Higher survival has been reported in those recurrent patients whose tumor was resected and in those in whom it could not be [7, 8, 10, 11]. However, it is unclear if that was a consequence of the resection or differences in the HCC biology. Most recurrences, however, are not resectable, either due to tumor metastases or the presence of multifocal liver recurrences. For the latter, there are few reports from the pre-Sorafenib era, before 2008 [12], including the present one, of systemic [13, 14] or regional chemotherapy by chemoembolization [15, 16].

Before Sorafenib, only chemoembolization had been shown to prolong survival for unresectable HCC in randomized clinical trials [17, 18] and that was the therapy used in this case series and in 2 other reports [15, 16]. There are arguments for and against chemoembolization in the post-transplant setting. The main concern is damage to the artery supplying the graft, leading to loss of the new liver. The author is unaware of any report of this calamity. The advantages are 2-fold, namely, the known tumor-shrinking effectiveness of chemoembolization and the absence of the complications of cirrhosis and accompanying portal hypertension in this setting, unlike in unresected HCC. Since the use of Sorafenib in HCC has not so far been shown to be associated with high response rates, the combination of chemoembolization plus Sorafenib in this setting of HCC recurrences in the transplanted liver in future patients would seem to be a reasonable therapy to evaluate.

**Table 1.** Chemoembolization in the transplanted liver

	Patient					
	1	2	3	4	5	6
Diagnosis	HCC	HCC	HCC	HCC	HCC	HCC
Time to recurrence, months	3	7	18	12	11	4
Chemotherapy						
Drug used	DDP	DDP	DDP	DDP	DDP	DDP
Cycles, n	3	5	9	8	4	4
Response	progressive	PR	CR	PR	progressive	stable
Cause of death	liver	mets	mets	mets	mets	mets
Survival after recurrence, months	13	19	50	30	18	12
Liver toxicity	0	0	0	0	0	+

DDP = Diaminodichlorocisplatin (cisplatin); mets = metastases; PR = partial response; CR = complete response.

## References

- Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–699.
- Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, Tzakis AG, Van Thiel DH, Carr B, Selby R: Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991;214:221–228.
- Van Thiel DH, Carr B, Iwatsuki S, Selby RR, Fung JJ, Starzl TE: The 11-year Pittsburgh experience with liver transplantation for hepatocellular carcinoma: 1981–1991. *J Surg Oncol Suppl* 1993;3:78–82.
- Ringe B, Pichlmayr R, Wittekind C, Tusch G: Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. *World J Surg* 1991;15:270–285.
- Carr BI, Nagalla S: Medical Therapy of HCC in Hepatocellular Carcinoma: Diagnosis and Treatment. Carr BI (ed). Humana Press, New York, 2009, pp 527–568.
- Carr BI, Kondragunta V, Buch S, Branch R: Therapeutic equivalence in survival for hepatic arterial chemoembolization and <sup>90</sup>Yttrium microspheres (Y90) treatments in unresectable HCC. *Cancer* 2010;116:1305–1314.
- Regalia E, Fassati LR, Valente U, Pulvirenti A, Damilano I, Dardano G, Montalto F, Coppa J, Mazzaferro V: Pattern and management of recurrent hepatocellular carcinoma after liver transplantation. *J Hepatobiliary Pancreat Surg* 1998;5:29–34.
- Roayaie S, Schwartz JD, Sung MW, et al: Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. *Liver Transpl* 2004;10:534–540.
- Schlitt HJ, Neipp M, Weimann A, et al: Recurrence patterns of hepatocellular and fibrolamellar carcinoma after liver transplantation. *J Clin Oncol* 1999;17:324–331.
- Zimmerman MA, Ghobrial RM, Tong MJ, Hiatt JR, Cameron AM, Hong J, Busuttill RW: Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators. *Arch Surg* 2008;143:182–188.
- Kornberg A, Kupper B, Tannapfel A, Katenkamp K, Thrum K, Habrecht O, Wilberg J: Long-term survival after recurrent hepatocellular carcinoma in liver transplant patients: clinical patterns and outcome variables. *Eur J Surg Oncol* 2010;36:275–280.
- Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390.

- 13 Lee JO, Kim DY, Lim JH, Seo MD, Yi HG, Oh DY, Im SA, Kim TY, Bang YJ: Palliative chemotherapy for patients with recurrent hepatocellular carcinoma after liver transplantation. *J Gastroenterol Hepatol* 2009;24:800–805.
- 14 Valdivieso A, Bustamante J, Gastaca M, Uriarte JG, Ventoso A, Ruiz P, Fernandez JR, Pijoan I, Testillano M, Suarez MJ: Management of hepatocellular carcinoma recurrence after liver transplantation. *Tranplant Proc* 2010;42:660–662.
- 15 Ko HK, Ko GY, Yoon HK, Sung KB: Tumor response to transcatheter arterial chemoembolization in recurrent hepatocellular carcinoma after living donor liver transplantation. *Korean J Radiol* 2007;8:320–327.
- 16 Zhou B, Shan H, Zhu KS, Jiang ZB, Guan SH, Meng XC, Zeng XC: Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. *J Vasc Interv Radiol* 2010;21:333–338.
- 17 Lo C, Ngan H, Tso WK, et al: Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164–1171.
- 18 Llovet J, Real M, Montana X, et al: Arterial embolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Lancet* 2002;359:1734–1739.